Trends in Cervical Cancer Screening

Thomas C. Wright, Jr. MD
Columbia University, New York
Cervical Cancer Screening

Topics to be covered

• Current status of cervical cancer prevention efforts in U.S.
Cervical Cancer in U.S.  
Statistics for 2008

- 11,070 cases - invasive cervical cancer
- 3,870 deaths from cervical cancer
- 1 out of 50 cancer-related deaths
- 0.4% of all female deaths

American Cancer Society - Facts and Figures 2008
## Apparent Cause of Cervical Cancers

*Data from Cancer Registries*

<table>
<thead>
<tr>
<th>Cause</th>
<th>Kaiser</th>
<th>Sweden</th>
</tr>
</thead>
<tbody>
<tr>
<td>No recent screen</td>
<td>56%</td>
<td>64%</td>
</tr>
<tr>
<td>Failure of Pap</td>
<td>32%</td>
<td>24%</td>
</tr>
<tr>
<td>Failure of follow-up</td>
<td>13%</td>
<td>11%</td>
</tr>
</tbody>
</table>

Leyden et al. JNCI 2005; 97: 675,
Andrae et al. JNCI 2008; 100: 622
Liquid-based Cytology

Recent review of literature

- All published studies from 1991 - 2007
- Selected studies in which Pap & LBC from same woman or similar cohorts
- Restricted to studies where ALL subjects had colposcopy or were RCT

Arbyn et al. (2008) Obstet Gynecol
Liquid-based Cytology

Conclusions of Arbyn review

• Only 8 studies fulfilled the criteria used to identify "high quality" studies

• Concluded that: "Liquid-based cytology is neither more sensitive nor more specific for detection of high-grade CIN compared with conventional Pap test"

Arbyn et al. (2008) Obstet Gynecol
False Negative Screening

Adenocarcinoma is a real problem

- Adenocarcinomas are becoming more frequently encountered
  
  Greater reductions in squamous lesions with screening
  Absolute increases in young women

- False negatives common since difficult to recognize and can occur in the canal
A Manhattan jury has awarded $11.8 million to the husband and children of a fashion-industry sales executive who died of cervical cancer that went undetected through several years of medical examinations and tests. The executive, Vicki Malouf, 45, died Aug. 9, 2001, her lawyer, Judith A. Livingston, said, because her gynecologist missed abnormalities that developed into full-blown cancer and the medical lab that she used misread the results of two Pap smears. Ms. Livingston said that on Monday the jury apportioned blame and
Cervical Cancer in U.S.  
*Clinical Perspective in 2009*

- Clear that cytology misses a significant proportion of cases of cervical cancer
- Adenocarcinomas which often occur in younger women are a growing concern
- Missed cases not only cause harm to patients, but are associated with a significant risk of litigation
Cervical Cancer Screening

Topics to be covered

• Current status of cervical cancer prevention efforts in U.S.

• Recommended uses of HPV DNA testing - *2006 Consensus Guidelines*
Recommended Uses of HPV

General caveats - 2006 Guidelines

- Test only for high-risk types of HPV
- No testing of adolescents for any reason
- Use only tests that have been both analytically and clinically validated as documented by FDA approval and/or peer-reviewed publications

HPV DNA Testing
Recommendations of 2006 Guidelines

- ASC-US in general population - preferred whenever LBC used
- LSIL in postmenopausal women - preferred if LBC used
- Post-colposcopy follow-up if no CIN 2,3 identified - acceptable approach
- Post-treatment of CIN 2,3 - acceptable
- Women with AGC - after initial colpo
Cervical Cancer Screening

Topics to be covered

- Current status of cervical cancer prevention efforts in U.S.
- Recommended uses of HPV DNA testing - 2006 Consensus Guidelines
- Screening women 30 yrs and older
Cervical Cancer Screening
American Cancer Society - 30+ yrs

- If three consecutive, negative Paps - can be screened at 2-3 yr intervals using cytology
- Alternatively, women can be screened every 3 yrs using combination of Pap and HPV DNA testing

Saslow et al. (2002) CA for Clinicians
Cervical Cancer Screening

ACOG - 30+ yrs

- Use of a combination of cervical cytology and HPV DNA screening is appropriate for women aged 30 yrs and older.
- If this combination is used, women negative on both should be rescreened no more frequently than every 3 yrs.

ACOG Practice Bulletin (2005)
Because HPV DNA testing is more sensitive than cervical cytology in detecting CIN 2 and CIN 3, women with negative concurrent test results can be reassured that their risk of unidentified CIN 2 and CIN 3 or cervical cancer is approximately 1 in 1,000."

Level A

ACOG Practice Bulletin (2005) Human Papillomavirus
HPV DNA Testing for Screening

Current status of science - 2009

- Large number of cross-sectional studies demonstrating superiority of HPV DNA testing compared to cytology - more sensitive and less variability than Pap
- Randomized screening trials are now being completed
- Data appears to be simply overwhelming
Sensitivity Pap for CIN 2,3

Germany  Mexico  South Africa  Switzerland  Canada
U.K.      Costa Rica  China  Italy
Sensitivity of HPV for CIN 2,3

Germany  Mexico  South Africa  Switzerland  Canada
U.K.  Costa Rica  China  Italy
Sensitivity of HPV vs Pap for CIN 2,3

Average gain is 28%!

Germany, Mexico, South Africa, Switzerland, Canada, U.K., Costa Rica, China, Italy
HPV for Screening
Joint European Cohort Study

24,295 women from 7 HPV screening trials in 6 European countries - age ranges varied between the trials with some including women < 30 yrs

Follow-up of women with ≥1 Pap or histopathology exam during follow-up

End-point; cumulative incidence of CIN 3+

Dillner et al. BMJ 2009
Cumulative Incidence CIN 3+

All women, including those in 20s

Dillner et al. BMJ 2009
Cumulative Incidence CIN 3+

Excluding Denmark and Tubingen

Dillner et al. BMJ 2009
The joint analysis consistently found a low six year cumulative incidence rate of CIN 3+ in women negative for HPV. Concluded that cervical screening strategies with HPV testing every six years is safe and effective.

Dillner et al. BMJ 2009
HPV for Screening
Women's preferences in U.S.

In-person or telephone interviews in 865 ethnically diverse women 50-80 yrs old from various clinics in San Francisco

Gave a short introduction on relationship of HPV to cervical cancer and test performance characteristics

Huang et al. J Gen Intern Med 2008
<table>
<thead>
<tr>
<th>Question asked</th>
<th>% &quot;Yes&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previously heard about HPV</td>
<td>30%</td>
</tr>
<tr>
<td>Previously had HPV test</td>
<td>7%</td>
</tr>
<tr>
<td>Want to be tested for HPV</td>
<td>64%</td>
</tr>
<tr>
<td>Would want to be tested if physician recommended</td>
<td>17%</td>
</tr>
</tbody>
</table>

Huang et al. J Gen Intern Med 2008

* in addition to the 64%
### HPV for Screening

**Women less than 65 yrs old**

<table>
<thead>
<tr>
<th>Question asked</th>
<th>% &quot;Yes&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>If HPV &amp; Pap (-), would 3 yr interval be acceptable to you</td>
<td>55%</td>
</tr>
<tr>
<td>Agree to 3 yr interval if physician recommended</td>
<td>12%</td>
</tr>
</tbody>
</table>

Huang *et al.*  J Gen Intern Med  2008

* in addition to the 64%
<table>
<thead>
<tr>
<th>Question asked</th>
<th>% &quot;Yes&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>If HPV &amp; Pap (-), would be willing to stop being screened</td>
<td>33%</td>
</tr>
<tr>
<td>Agree to stop screening if physician recommended</td>
<td>19%</td>
</tr>
</tbody>
</table>

Huang et al. J Gen Intern Med 2008

* in addition to the 64%
HPV Testing for Screening in U.S.  
Clinical Perspective in 2009

- Clear that HPV is more sensitive than cytology
- HPV negative women have a low long-term risk for development of CIN 3+
- Reducing screening interval to 3 - 6 yrs appears safe when HPV testing is used
- Patients appear to want HPV testing
Cervical Cancer Screening

Topics to be covered

• Current status of cervical cancer prevention efforts in U.S.
• Recommended uses of HPV DNA testing - 2006 Consensus Guidelines
• Screening women 30 yrs and older
• HPV testing without Pap for screening
HPV DNA Testing - Screening

Will we move totally away from cytology?

- It appears that cytology adds little to HPV testing *alone* for screening women $\geq 30$ yrs

- In the U.S. many groups are heavily vested in maintaining cytology - *pathologists, cytotechnicians, laboratories, some clinicians and patients, state regulations*

- Screening with HPV alone will likely be utilized in Europe before the U.S. adopts
HPV for Screening

Swedish Randomized Screening Trial

6,257 women 32-38 yrs had conventional cytology plus HPV testing (*PCR with *GP5+/6*)

If Pap abnormal, follow-up by std practice

HPV (+) / Pap (-) retested with BOTH at 12 mos - *colpo if persistently HPV (+)*

Follow-up by registry data for 4.1 yrs

Naucler et al. JNCI 2009

*same type of HPV*
# HPV for Screening - CIN 2+

**Swedish Randomized Screening Trial**

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Sens</th>
<th>PPV</th>
<th># Tests*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pap alone</td>
<td>71</td>
<td>42</td>
<td>101</td>
</tr>
<tr>
<td>HPV alone</td>
<td>95</td>
<td>19</td>
<td>75</td>
</tr>
<tr>
<td>Pap &amp; HPV</td>
<td>100</td>
<td>18</td>
<td>144</td>
</tr>
<tr>
<td>HPV with &quot;reflex&quot; Pap</td>
<td>95</td>
<td>38</td>
<td>85</td>
</tr>
<tr>
<td>HPV with &quot;reflex&quot; Pap and 16/18</td>
<td>95</td>
<td>28</td>
<td>81</td>
</tr>
</tbody>
</table>

Naucler et al. JNCI 2009

* to detect one case of CIN 2+
Cervical Cancer Screening

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- HPV testing without Pap for screening
- Use of HPV genotyping
Risk Assessment Factors

*Use of genotyping assays*

- There is some data suggesting that stratifying high-risk HPV positive women by specific HPV genotypes could lead to better clinical outcomes
- However, rather limited clinical data and not clear which genotypes would give best results
- No FDA-approved genotyping test
Predictive Value of HPV Type

*NCI-Kaiser follow-up study*

- 20,817 women with adequate cytology at enrollment (*1994-1996*)
- Tested frozen cervical lavage samples for HPV using PCR assay
- Follow-up was with cytology and "standard workup" of abnormals

*Khan et al. JNCI (2005)*
Development of CIN 3 on Follow-up

- HPV 16
- HPV 18
- High-risk HPV - other types
- High-risk negative

Khan et al. (2005) JNCI
2006 Consensus Guidelines

Recommendations on use of genotyping

- State genotyping should not be used until there is an FDA-approved test
- Once available, genotyping for HPV 16 and 18 can be used to determine which HPV(+) / Pap (-) women need colposcopy

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